Total Synthesis of the Biphenomycins; V.[1] Synthesis of Biphenomycin A[2]

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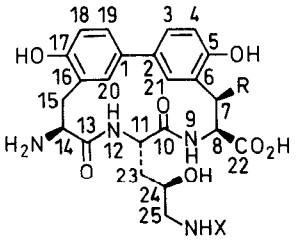
Dedicated to Professor Ernst Bayer on the occasion of his 65th birthday

The total synthesis of biphenomycin A is described. Two of the five stereogenic centres were formed by enantioselective hydrogenation of the corresponding didehydroamino acids using the rhodium-DIPAMP catalyst and the two stereogenic centres of the α-amino-β-hydroxy unit were created by enantioselective hydrogenation using the ruthenium-BINAP catalyst or via a stereoselective aldol condensation, respectively. The biphenyl structural element was constructed by a palladium(0)-catalyzed coupling reaction. The 15-membered ansa ring was closed in 85% yield by use of the appropriate, linear pentafluorophenyl ester in the two phase system chloroform/aqueous sodium hydrogen carbonate.

We have previously reported the preparation of diisotyrosine dimethyl ether, the construction of a simple model compound for biphenomycin B,[3] and the total synthesis of the cyclopeptide biphenomycin B **(1b)**.[4,5] The latter compound exhibits a highly potent antibiotic activity against Gram-positive, β-lactam-resistant bacteria. In the meantime, competing groups have reported[6-8] several preparations of simpler analogues of these therapeutically interesting antibiotics but no total syntheses of the natural compounds were achieved by other research teams. The major metabolite from the culture filtrate of *Streptomyces griseorubiginosus* No. 43708 is biphenomycin A **(1a)**[9-11] which contains an additional stereogenic centre, i.e. the biphenyl unit represents the dimer-type coupling product of (*S*)-*o*-hydroxyphenylalanine with (2*S*,3*R*)-*o*-hydroxyphenylserine.[12] We have also published the synthesis of biphenomycin A[15] **(1a)** in a preliminary communication. In that report, the phenylserine part was constructed with the help of the Evans method. We now present the experimental details and describe a further method for the construction of the α-amino-β-hydroxy acid via ruthenium-BINAP-catalyzed hydrogenation of an appropriate α-amino-β-oxo acid.



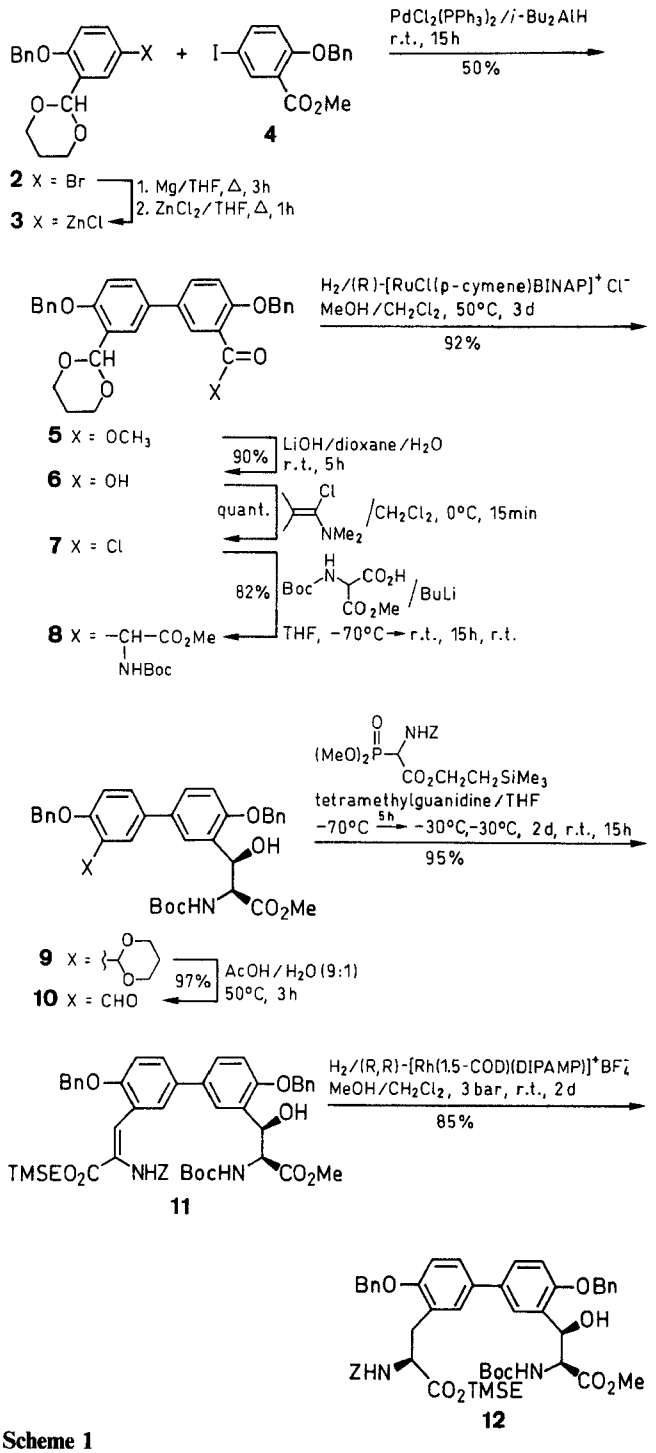
1a R = OH, X = H
b R = H, X = H
c R = OH, X = Arg

The biphenyl moiety is constructed by the palladium-(0)-catalyzed coupling reaction of an arylboronic acid[16] or an arylzinc derivative,[17] respectively, with the appropriate aryl bromide. In the course of the synthesis, it is necessary to mask two phenolic hydroxy groups, two amino groups, two hydroxy groups, and one carboxy group with protecting groups that are compatible with those of the amino functions of the hydroxyornithine and the one carboxy function of the hydroxydiisotyrosine which have to be cleaved in the course of the construction of the peptide. In the ring-closure reaction, the two hydroxy groups remain unmasked.

Synthesis of Hydroxydiisotyrosine by Ruthenium-BINAP-Catalyzed Hydrogenation

The present preparation of a protected (*R*)-hydroxy-(*S,S*)-diisotyrosine is based on the enantio- and diastereoselective hydrogenation of a racemic α-acylamino-β-oxo acid ester which gives rise to an optically active α-acylamino-β-hydroxy acid ester with the *threo* configuration by use of Noyori's catalyst system.[18]

The reaction sequence is shown in Scheme 1. Starting material is the biphenyl compound **5**, easily obtained by palladium(0)-coupling[17] from the zinc derivative **3**, which is prepared in turn from the bromide **2**, with the iodide **4**. The planned conversion of the carboxylate to a β-oxo ester, the oxime formation, and the reduction to the α-amino-β-oxo acid ester failed at the reduction stage. A smooth, one-step synthesis of the α-amino-β-oxo ester **8** is provided by the reaction of the carboxylic acid chloride **7** with the dilithium derivative of methyl *tert*-butoxycarbonylaminomalonate. This reaction is generally suitable for the preparation of α-acylamino-β-oxo esters. For the hydrogenation of the β-oxo compound **8**, we used the catalyst (*R*)-[RuCl(*p*-cymene) (BINAP)]$^+$Cl$^-$ (BINAP = 2,2-bis(diphenylphosphino)-1,1-binaphthyl) which is easily accessible by simply mixing the components.[19] High enantio- and diastereoselectivities are only achieved when the solutions of the substrates and catalyst contain only very little methanol. When the methanol content increases, the hydrogenation rate increases while the stereoselectivity decreases. After cleavage of the acetal to the aldehyde **10**, condensation with a suitably protected (dialkoxyphosphoryl)glycine ester[20] furnished the (*Z*)-didehydroamino acid derivative **11** in very good diastereoselectivity[21] ($Z > 98\%$). The hydrogenation with the optically active catalyst[22] (*R,R*)-[Rh(1,5-COD)-(DIPAMP)]$^+$ [BF_4]$^-$ {COD = cycloocta-1,5-diene, DIPAMP = (*R,R*)-1,2-bis[2-(2-methoxyphenyl)phenylphosphino]ethane} proceeded with high enantio- or diastereoselectivity, respectively, to yield the hydroxydiisotyrosine **12**. The steric course of these reactions can be monitored by chromatography. The diastereoselectivity in the BINAP hydrogenation was estimated by chromatographic separation of the isomers as 95:5 (*erythro: threo*) and the enantioselectivity as 95:5 (*R,S: S,R*, HPLC Pirkle column). The mixture of enantiomers was employed for further reactions. A preparative separation was successful only at the stage of the diastereomeric dipeptides **21a** and **21b**.

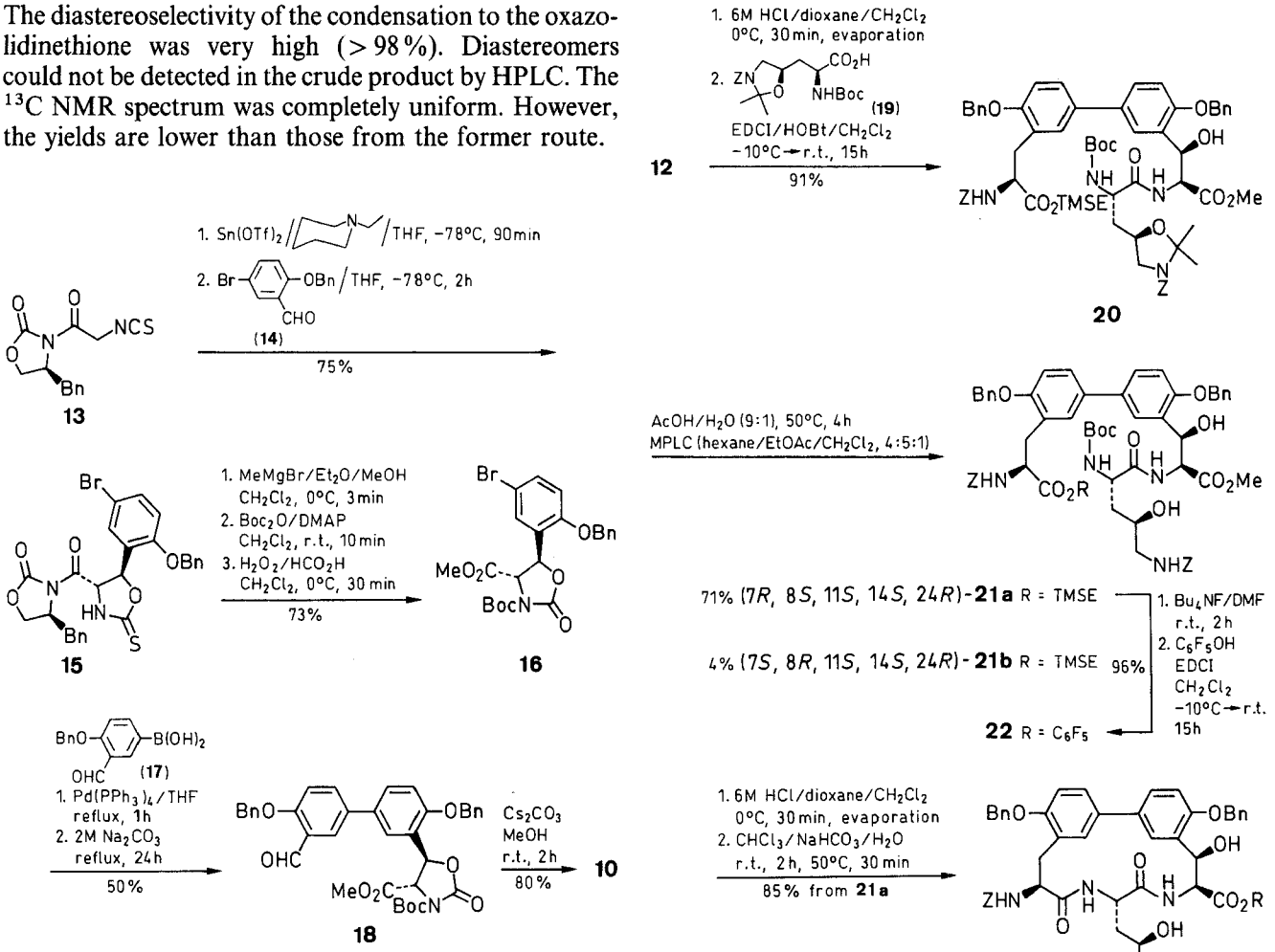


Scheme 1

Synthesis of Hydroxydiisotyrosine by the Enolate Method

The reaction sequence is illustrated in Scheme 2. The aryl bromide **16** represents a completely protected 2-hydroxy-5-bromophenylserine and can be prepared via **15** by the Evans method.[23] The palladium(0)-catalyzed coupling of **16** with the boronic acid **17** containing an unprotected aldehyde function gives rise to the biphenyl derivative **18**. The stated reaction conditions must be followed exactly during the preparation of the boronic acid. The Boc-oxazolidinone **18** can be cleaved easily to **10** by treatment with cesium carbonate. The aldehyde is then converted to the hydroxydiisotyrosine derivative **12** as described above.

The diastereoselectivity of the condensation to the oxazolidinethione was very high (> 98%). Diastereomers could not be detected in the crude product by HPLC. The ^{13}C NMR spectrum was completely uniform. However, the yields are lower than those from the former route.



Scheme 2

Scheme 3

Construction of the Linear Peptide and the Ring Closure Reaction

The construction of the linear substrate for the ring closure reaction was achieved in analogy to the synthesis of biphenomycin B starting from the hydroxyornithine derivative **19**[24] (Scheme 3). The only exception is that the free carboxy group is now protected as a methyl ester (instead of a benzyl ester as in the biphenomycin B synthesis). The unwanted enantiomer from the BINAP hydrogenation was removed at the stage of the diastereomeric dipeptide esters **21a** and **21b**. The ring closure reaction of the ω-aminopentafluorophenyl ester in the two phase system chloroform/aqueous sodium hydrogen carbonate occurred within 3 hours to give a yield of 85%. This procedure has been our method of choice for several years.[25] Alternative processes in the synthesis of simpler model compounds operating under high dilution conditions furnish lower yields (Lit.[6]: 37%; Lit.[7]: 40%; Lit.[8]: 21%). After saponification of the methyl ester, the benzyl protecting groups were removed by treatment with trimethylsilyl bromide/thioanisole in trifluoroacetic acid.[26] The synthetic product thus obtained was separated by reversed-phase chromatography and then lyophilized. It is identical in all respects with the naturally occurring compound.

^1H NMR spectra were recorded on a Bruker AC-F (250 MHz), ^{13}C NMR spectra on a Bruker AC-F (63 MHz) spectrometer. Optical rotation values were determined with a Perkin-Elmer 241 polarimeter. Melting points (Reichert microscope) are uncorrected. TLC was done on silica gel (Merck Silica 60 F_{254} sheets) and medium pressure column chromatography using Merck LiChroprep Si 60 (15–25 μ). HPLC was carried out with a LKB Instrument and a silica gel column (Merck LiChroCART (250-4 mm), LiChroSorb Si 60,7 μ, or LiChroSorb RP 18,7 μ). Prep-HPLC was done with a Latek (Prep 5000) Instrument using a column (300 × 20 mm, RP 18, 10 μ, Fa. Latek). The MS spectra were recorded on a Finnigan MAT 95. Compounds **4–6, 8–12, 15–18, 20, 21a** and **23** gave satisfactory microanalyses (C ± 0.32, H ± 0.17, N ± 0.17, Br ± 0.07, I ± 0.18).

2-Benzyloxy-5-iodobenzoic Acid:

To a stirred solution of 2-benzyloxy-5-iodobenzaldehyde[5] (30 g, 88.8 mmol) and amidosulfonic acid (12.06 g, 124.2 mmol) in dioxane/H_2O (240 mL, 5:1), a solution of $NaClO_4$ (12 g, 80%, 106.2 mmol) in H_2O (160 mL) was added dropwise at r.t. The

mixture was stirred for 30 min, dioxane was evaporated and the residue was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. Recrystallization of the residue from hexane afforded 2-benzyloxy-5-iodobenzoic acid; yield 28.6 g (92%); mp 72–75°C.

^1H NMR ($CDCl_3$/TMS): δ = 5.28 (s, 2H), 6.89 (d, 1H, J = 8.8 Hz), 7.42 (s, 5H), 7.81 (dd, 1H, J = 2.5, 8.7 Hz), 8.46 (d, 1H, J = 2.4 Hz), 10.7 (br s, 1H).

Methyl 2-Benzyloxy-5-iodobenzoate (4):
A solution of 2-benzyloxy-5-iodobenzoic acid (28 g, 79 mmol) in MeOH (30 mL) was treated with diazomethane (ca. 0.5 M solution in Et_2O) until the mixture remained yellow. After addition of AcOH (2 drops to decompose the excess diazomethane), the solvent was evaporated and the residue was distilled under reduced pressure to give the methyl ester **4**; yield: 28.5 g (98%); bp 175°C/0.001 mbar.

^1H NMR ($CDCl_3$/TMS): δ = 3.89 (s, 3H), 5.16 (s, 2H), 6.77 (d, 1H, J = 8.8 Hz), 7.25–7.50 (m, 5H), 7.68 (dd, 1H, J = 2.4, 8.7 Hz), 8.09 (d, 1H, J = 2.4 Hz).

4,4′-Dibenzyloxy-3-(1,3-dioxan-2-yl)-3′-(methoxycarbonyl)biphenyl (5):
To magnesium turnings (2.48 g, 102 mmol) in THF (10 mL), one third of a solution of **2**[5] (35.57 g, 101.9 mmol) in THF (100 mL) was added. The mixture was heated and the reaction was initiated with a crystal of iodine. The remaining aryl halide solution was added dropwise under reflux. After refluxing for 2 h, the solution was cooled to r.t.. To this Grignard reagent, anhydrous $ZnCl_2$ (13.9 g, 102 mmol) was added cautiously and the mixture was refluxed for 1 h.

In a second flask 1 M solution of diisobutylaluminum hydride (DIBAL-H) (6.79 mL in hexane) was added to a suspension of $(Ph_3P)_2PdCl_2$ (2.38 g, 3.39 mmol) in THF (100 mL). The mixture was stirred for 10 min, a solution of **4** (25 g, 67.9 mmol) in THF (100 mL) was added followed by the arylzinc halide suspension **3** prepared above. The mixture was stirred for 15 h at r.t. and the solvent was evaporated. The residue was dissolved in a mixture of CH_2Cl_2 (300 mL) and sat. aq NH_4Cl (300 mL). The separated aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL), the combined organic layers were dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography over silica gel (eluent: hexane/EtOAc/CH_2Cl_2 7:2:1) and recrystallized from EtOAc/hexane to give **5**; yield: 17.2 g (50%); mp 151–154°C.

^1H NMR ($CDCl_3$/TMS): δ = 1.53 (m, 1H), 2.27 (m, 1H), 3.92 (s, 3H), 4.01 (dt, 2H, J = 2.2, 12.3 Hz), 4.27 (dd, 2H, J = 4.2, 11.7 Hz), 5.14 (s, 2H), 5.20 (s, 2H), 5.97 (s, 1H), 6.97 (d, 1H, J = 8.7 Hz), 7.03 (d, 1H, J = 8.7 Hz), 7.25–7.52 (m, 11H), 7.63 (dd, 1H, J = 2.4, 8.7 Hz), 7.85 (d, 1H, J = 2.4 Hz), 8.04 (d, 1H, J = 2.4 Hz).

4,4′-Dibenzyloxy-3-(1,3-dioxan-2-yl)-3′-carboxybiphenyl (6):
A mixture of **5** (13.2 g, 25.8 mmol) in dioxane (200 mL) and LiOH · H_2O (2.17 g, 51.7 mmol) in H_2O (70 mL) was treated in an ultrasonic bath at r.t. for 5 h. Then the mixture was stirred at 50°C for 15 h. The dioxane was evaporated, the aqueous residue was acidified with 1 M H_2SO_4 (35 mL) and extracted with EtOAc (3 × 50 mL). The organic layers were dried ($MgSO_4$) and evaporated in vacuo. The product was purified by column chromatography on silica gel (eluent: hexane/EtOAc/CH_2Cl_2, 2:7:1) and recrystallized from EtOAc/hexane to give **6**; yield: 11.5 g (90%); mp 142–144°C.

^1H NMR ($CDCl_3$/TMS): δ = 1.44 (m, 1H), 2.28 (m, 1H), 4.02 (dt, 2H, J = 2.1, 12.2 Hz), 4.27 (dd, 2H, J = 5.0, 11.0 Hz), 5.15 (s, 2H), 5.32 (s, 2H), 5.97 (s, 1H), 6.99 (d, 1H, J = 8.6 Hz), 7.15 (d, 1H, J = 8.7 Hz), 7.25–7.50 (m, 11H), 7.77 (dd, 1H, J = 2.5, 8.6 Hz, 7.89 (d, 1H, J = 2.5 Hz), 8.44 (d, 1H, J = 2.5 Hz), 10.85 (br s, 1H).

(tert-Butoxycarbonylamino)malonic Acid Monomethyl Ester:
To a stirred solution of dimethyl aminomalonate hydrochloride (10 g, 54.5 mmol) and di-*tert*-butyl dicarbonate (11.9 g, 54.5 mmol) was added 1 M aq $KHCO_3$ (55 mL) over a period of 1 h. The mixture was stirred for 24 h at r.t., dioxane was evaported in vacuo and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by silica gel chromatography (eluent: hexane/EtOAc, 7:3) to give dimethyl (*tert*-butyloxycarbonylamino)malonate; yield: 11 g (81%).

^1H NMR ($CDCl_3$/TMS): δ = 1.45 (s, 9H), 3.82 (s, 6H), 5.00 (d, 1H, J = 7.8 Hz), 5.59 (br d, 1H, J = 7.5 Hz).

A solution of dimethyl (*tert*-butyloxycarbonylamino)malonate (10.5 g, 42.5 mmol) in dioxane (50 mL) was treated with 1 M aq. NaOH (42.5 mL) over a period of 3 h. The mixture was stirred for 15 h at r.t. and dioxane was evaporated in vacuo. The aqueous residue was washed with Et_2O (50 mL), then diluted with EtOAc (50 mL), acidified with 1 M H_2SO_4 (25 mL) at 0°C (stirring), separated and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated and dried in vacuo (0.001 mbar); yield: 9 g (91%); oil.

$C_9H_{15}NO_6$	calc.	C 46.35	H 6.48	N 6.01
(233.2)	found	46.43	6.74	6.34

^1H NMR (DMSO-d_6/TMS): δ = 1.38 (s, 9H), 3.68 (s, 3H), 4.74 (d, 1H, J = 8.9 Hz), 7.48 (d, 1H, J = 8.0 Hz).

4,4′-Dibenzyloxy-3-[(*R,S*)-2-(*tert*-butoxycarbonylamino)-2-methoxycarbonyl)-1-oxoethyl]-3′-(1,3-dioxan-2-yl)biphenyl (8):
To a stirred solution of **6** (3.7 g, 7.45 mmol) in anhydrous CH_2Cl_2 (10 mL), 1-chloro-1-(*N,N*-dimethylamino)-2-methyl-1-propene[27] (1 mL, 7.49 mmol) was added at 0°C. The mixture was stirred at this temperature for 15 min and then used immediately without isolation of the acid chloride **7**. In a second flask, a solution of (*tert*-butyloxycarbonylamino)malonic acid monomethyl ester (3.5 g, 14.9 mmol) in anhydrous THF (100 mL) was treated with 1.6 M BuLi in hexane (18.6 mL, 29.8 mmol) at −70°C. After stirring for 20 min at −70°C, the acid chloride **7** was added over a period of 10 min. The mixture was allowed to warm to r.t. slowly, stirred well, kept at r.t. for 15 h and concentrated in vacuo. The residue was dissolved in EtOAc (50 mL), washed with 0.5 M H_2SO_4 (5 mL, 0°C) and 1 M aq $KHCO_3$ (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by MPLC (eluent: hexane/EtOAc/CH_2Cl_2, 7:2:1) to give **8** as a colourless foam; yield: 4.1 g (82%).

^1H NMR ($CDCl_3$/TMS): δ = 1.43 (s, 9H), 1.95 (m, 1H), 2.27 (m, 1H), 3.59 (s, 3H), 4.00 (dt, 2H, J = 2.3, 12.0 Hz), 4.26 (dd, 2H, J = 5.0, 10.9 Hz), 5.14 (s, 2H), 5.26 (s, 2H), 5.83 (d, 1H, J = 7.8 Hz), 5.95 (s, 1H), 6.08 (d, 1H, J = 8.0 Hz), 6.96 (d, 1H, J = 8.6 Hz), 6.98 (d, 1H, J = 8.6 Hz), 7.25–7.50 (m, 11H), 7.65 (dd, 1H, J = 2.4, 8.6 Hz), 7.83 (d, 1H, J = 2.4 Hz), 7.93 (d, 1H, J = 2.4 Hz).

4,4′-Dibenzyloxy-3-[(*S*)-2-(*tert*-butoxycarbonylamino)-2-methoxycarbonyl-(*R*)-1-hydroxyethyl]-3′-(1,3-dioxan-2-yl)biphenyl (9):
A solution of **8** (1 g, 1.5 mmol) and a solution of (*R*)-(RuCl(*p*-cymene)BINAP]Cl (0.3 mL, 0.038 molar in MeOH/CH_2Cl_2, 3:1)[19] in CH_2Cl_2 (10 mL) was hydrogenated under stirring in a high pressure vessel (Roth) at 50 bar H_2 and 50°C for 3 d. After evaporation of the solvent, the residue was purified by MPLC (hexane/EtOAc/CH_2Cl_2, 6:3:1) to give the *anti*-diastereoisomers (50 mg) and the desired *syn*-1-hydroxy-2-amino-diastereoisomers **9** (870 mg); total yield: 920 mg (92%); ds = 95%; ee = 90%, enantiomeric excess of the *syn*-product was determined by HPLC (Pirkel DNPG-column, eluent: hexane/EtOAc, 6:4; (1*S*,2*R*)-enantiomer: R_t = 6.5 min, (1*R*,2*S*)-enantiomer: R_t = 8 min).

^1H NMR ($CDCl_3$/TMS): δ = 1.27 (s, 9H), 1.75 (m, 1H), 2.18 (m, 1H), 3.40 (s, 3H), 3.45 (br, 1H), 3.93 (dt, 2H, J = 2.2, 12.2 Hz), 4.19 (dd, 2H, J = 4.2, 11.7 Hz), 4.69 (m, 1H), 5.06 (s, 4H), 5.23 (br s, 1H), 5.31 (d, 1H, J = 8.0 Hz), 5.88 (s, 1H), 6.86 (d, 1H, J = 8.5 Hz), 6.88 (d, 1H, J = 8.6 Hz), 7.20–7.50 (m, 12H), 7.46 (d, 1H, J = 2.2 Hz), 7.75 (d, 1H, J = 2.4 Hz).

4,4'-Dibenzyloxy-3-[(*S*)-2(*tert*-butoxycarbonylamino)-2-methoxycarbonyl)-(*R*)-1-hydroxyethyl]biphenyl-3'-carbaldehyde (10):
A solution of **9** (800 mg; 1.2 mmol) in AcOH/H_2O (20 mL, 9/1) was stirred at 50 °C for 3 h. After evaporation of the solvent, the residue was dissolved in EtOAc, washed with 1 M aq $KHCO_3$ (20 mL), dried ($MgSO_4$) and evaporated. The product was purified by silica gel chromatography (eluent: hexane/EtOAc/CH_2Cl_2, 6:3:1) and dried in vacuo (0.001 mbar) to give **10**; yield: 710 mg (97%); colourless foam; $[\alpha]_D^{20}$ + 23.4° (*c* = 0.96, $CHCl_3$), 90% ee [**10**, prepared by *Evans method:* $[\alpha]_D^{20}$ + 26.1° (*c* = 0.8, $CHCl_3$)].

^{1}H NMR ($CDCl_3$/TMS): δ = 1.22 (s, 9H), 2.94 (br s, 1H), 3.74 (s, 3H), 4.81 (d, 1H, *J* = 9.5 Hz), 5.06–5.18 (m, 4H), 5.40 (d, 1H, *J* = 9.6 Hz), 5.66 (br s, 1H), 6.98 (d, 1H, *J* = 8.5 Hz), 7.09 (d, 1H, *J* = 8.7 Hz), 7.25–7.50 (m, 11H), 7.63 (d, 1H, *J* = 2.2 Hz), 7.72 (dd, 1H, *J* = 2.5, 8.7 Hz), 8.03 (d, 1H, *J* = 2.2 Hz), 10.58 (s, 1H).

4,4'-Dibenzyloxy-3-[(*S*)-2-(*tert*-butoxycarbonylamino)-2-(methoxycarbonyl)-(*R*)-1-hydroxyethyl]-3'-[(*Z*)-2-(benzyloxycarbonylamino)-2-(trimethylsilylethoxycarbonyl)vinyl]biphenyl (11):
To a solution of 3'-trimethylsilylethyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate[20,21] (690 mg, 1.65 mmol) and tetramethylguanidine (173 mg, 1.5 mmol) in anhydrous THF (5 mL) **10** (660 mg, 1.08 mmol) was added at −70 °C. The mixture was allowed to warm up to −30 °C within 5 h and was kept at this temperature for 2 d. After another 15 h at r.t., the solution was diluted with EtOAc (30 mL), washed with 0.5 M H_2SO_4 (3 mL) and 1 M aq $KHCO_3$ (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was filtered through silica gel (eluent: hexane/EtOAc/CH_2Cl_2, 4.5:4.5:1) to yield the didehydroamino acid derivative **11** (925 mg, 95%) which was used for the DIPAMP-hydrogenation without further purification. *E*/*Z* ratio = 2:98; purity > 99% determined by HPLC (R_{tE} = 5.37 min, R_{tZ} = 6.53 min, eluent: hexane/EtOAc, 70:30).

^{1}H NMR ($CDCl_3$/TMS): δ = 0.03 (s, 9H), 0.99–1.04 (m, 2H), 1.21 (s, 9H), 3.73 (s, 3H), 4.27 (t, 2H, *J* = 8.4 Hz), 4.79 (d, 1H, *J* = 8.4 Hz), 5.07–5.27 (m, 7H), 5.45 (br s, 1H), 5.60 (br s, 1H), 6.87–6.99 (m, 3H), 7.22–7.55 (m, 19H), 7.74 (s, 1H).

3-[(*S*)-2-(Benzyloxycarbonylamino)-2-(trimethylsilylethoxycarbonyl)ethyl]-3'-[(*S*)-2-(*tert*-butoxycarbonylamino)-2-(methoxycarbonyl)-(*R*)-1-hydroxyethyl]-4,4'-dibenzyloxybiphenyl (12):
A solution of **11** (850 mg, 0.94 mmol) in MeOH/CH_2Cl_2 (16 mL, 3:1), containing (*R,R*)-[Rh(1,5-COD) (DIPAMP)]$^+$ BF_4^- (20 mg), was hydrogenated (3 bar) at r.t. over 2 d. The mixture was evaporated and the residue was filtered through silica gel (eluent: hexane/EtOAc/CH_2Cl_2 7:2:1); yield: 720 mg (85%); $[\alpha]_D^{20}$ + 22.5° (*c* = 1.3, $CHCl_3$). Compound **12** prepared by Evans method: $[\alpha]_D^{20}$ + 24.2 (*c* = 0.88, $CHCl_3$).

^{1}H NMR ($CDCl_3$/TMS): δ = −0.01 (s, 9H), 0.90 (t, 2H, *J* = 8.4 Hz), 1.25 (s, 9H), 2.32 (br s, 1H), 3.09 (dd, 1H, *J* = 8.6, 13.6 Hz), 3.25 (dd, 1H, *J* = 4.8, 13.6 Hz), 3.74 (s, 3H), 4.04–4.24 (m, 2H), 4.56–4.61 (m, 1H), 4.82 (br d, 1H, *J* = 7.4 Hz), 4.95–5.18 (m, 6H), 5.37 (d, 1H, *J* = 8.9 Hz), 5.62 (m, 2H), 6.93 (dd, 2H, *J* = 2.0, 8.5 Hz), 7.15–7.50 (m, 18H), 7.56 (d, 1H, *J* = 2.0 Hz).

(*S*)-4-Benzyl-3-[(*R*)-5-(2-benzyloxy-5-bromo)phenyl-2-thioxo-(*S*)-4-oxazolidinylcarbonyl]oxazolidin-2-one (15):
To a suspension of $Sn(OTf)_2$ (1.43 g, 2.99 mmol) in THF (30 mL), *N*-ethylpiperidine (511 μL, 3.71 mmol) and (4*S*)-4-benzyl-3-isothiocyanatoacetyl-2-oxazolidinone (**13**;[22] 961 mg, 2.99 mmol) in THF (3 mL) were added at −78 °C. The resulting yellow solution was stirred for another 90 min at −78 °C, then 2-benzyloxy-5-bromobenzaldehyde (**14**;[5] 721 mg, 2.47 mmol) was added and stirring was continued for 2 h. To the stirred cold solution, 1 M NH_4Cl (30 mL) was added and the mixture was allowed to warm to r.t. The solvent was distilled and the residue was treated with a mixture of EtOAc (200 mL) and 1 M $KHSO_4$ (100 mL). The organic layer was separated, dried ($MgSO_4$), concentrated and filtered through silica gel using hexane/EtOAc (7:3) to afford the product **15**, pure enough for further reactions. For analytical data a sample (100 mg) was purified by MPLC (eluent: hexane/EtOAc, 75:25); yield: 1.05 g (75%); $[\alpha]_D^{20}$ + 102.9° (*c* = 0.97, $CHCl_3$).

^{1}H NMR ($CDCl_3$/TMS): δ = 2.83 (dd, 1H, *J* = 8.2, 13.5 Hz), 3.10 (dd, 1H, *J* = 3.0, 13.5 Hz), 3.99 (dd, 1H, *J* = 8.0, 8.2 Hz), 4.02 (m, 1H), 4.16 (dd, 1H, *J* = 2.1, 8.2 Hz), 4.92 (d, 1H, *J* = 10.9 Hz), 4.99 (m, 1H), 5.02 (d, 1H, *J* = 10.9 Hz), 6.66 (d, 1H, *J* = 4.4 Hz), 6.89 (d, 1H, *J* = 8.8 Hz), 7.11–7.13 (m, 2H), 7.27–7.60 (m, 11H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 188.02, 165.15, 153.66, 153.56, 135.53, 134.10, 132.86, 129.44, 129.15, 128.63, 128.54, 128.45, 127.81, 113.87, 113.24, 78.00, 70.76, 67.40, 63.67, 54.84, 37.24.

(*R*)-5-(2-Benzyloxy-5-bromo)phenyl-3-*tert*-butoxycarbonyl-(*S*)-4-(methoxycarbonyl)oxazolidin-2-one (16):
To MeOH (5 mL), 3 M MeMgBr in Et_2O (0.91 mL) was added. The resulting suspension was added to a solution of **15** (1.44 g, 2.5 mmol) in a mixture of MeOH (10 mL) and CH_2Cl_2 (10 mL) at 0 °C. Stirring was continued for 3 min, then 1 M $KHSO_4$ (10 mL) was added and the organic solvent was distilled. The residue was extracted with CH_2Cl_2 (2 × 50 mL), the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Recrystallization from hexane/EtOAc gave analytically pure (*R*)-5-(2-benzyloxy-5-bromo)phenyl (*S*)-4-(methoxycarbonyl)oxazolidin-2-thione; yield: 950 mg (90%); mp 79–80 °C; $[\alpha]_D^{20}$ + 21.8° (*c* = 0.45, $CHCl_3$).

^{1}H NMR ($CDCl_3$/TMS): δ = 3.58 (s, 3H), 4.45 (d, 1H, *J* = 5.4 Hz), 5.05 (s, 2H), 6.14 (d, 1H, *J* = 5.4 Hz), 6.88 (d, 1H, *J* = 8.6 Hz), 7.35–7.48 (m, 7H), 8.06 (s, br, 1H).

To a solution of the above oxazolidin-2-thione (200 mg, 0.47 mmol) in CH_2Cl_2 (20 mL), di-*tert*-butyldicarbonate (114 mg, 0.52 mmol) and a catalytical amount of DMAP were added. After 10 min, the resulting organic solution was diluted with CH_2Cl_2 (50 mL) and washed with 1 M $KHSO_4$ (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford the (*R*)-5-(2-benzyloxy-5-bromo)phenyl-3-*tert*-butoxycarbonyl-(*S*)-4-(methoxycarbonyl)oxazolidin-2-thione, pure enough for further reactions. For analytical data a sample (100 mg) was purified by MPLC (eluent: hexane/EtOAc, 8:2); yield: 221 mg (90%); $[\alpha]_D^{20}$ −3.2° (*c* = 0.46, $CHCl_3$).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.47 (s, 9H), 3.58 (s, 3H), 4.80 (d, 1H, *J* = 4.9 Hz), 5.09 (d, 2H, *J* = 1.3 Hz), 5.73 (d, 1H, *J* = 4.9 Hz), 6.88 (d, 1H, *J* = 8.5 Hz), 7.34–7.49 (m, 7H).

To a solution of (*R*)-5-(2-benzyloxy-5-bromo)phenyl-3-*tert*-butoxycarbonyl-(*S*)-4-(methoxycarbonyl)oxazolidin-2-thione (221 mg, 0.42 mmol) in CH_2Cl_2 (10 mL), 30% H_2O_2 (1 mL) and 95% HCO_2H (1 mL) were added at 0 °C. Stirring was continued for 30 min, then CH_2Cl_2 (50 mL) and 1 M Na_2CO_3 (100 mL) were added. The organic layer was separated, dried ($MgSO_4$) and concentrated in vacuo. The residue was crystallized from hexane/EtOAc to afford **16**; yield: 193 mg (73% from **15**); $[\alpha]_D^{20}$ + 5.5° (*c* = 0.36, $CHCl_3$).

^{1}H NMR ($CDCl_3$/TMS): δ = 1.46 (s, 9H), 3.54 (s, 3H), 4.56 (d, 1H, *J* = 4.1 Hz), 5.09 (s, 2H), 5.55 (d, 1H, *J* = 4.1 Hz), 6.88 (d, 1H, *J* = 9.3 Hz), 7.30–7.46 (m, 7H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.24, 154.44, 150.90, 148.47, 135.54, 133.32, 129.37, 128.82, 128.55, 127.82, 127.27, 113.83, 113.47, 84.12, 72.54, 70.87, 62.66, 52.83, 27.82.

4-Benzyloxy-3-formylphenylboronic Acid (17):
To magnesium turnings (2.78 g, 115 mmol) one third of a solution of 2-(2'-benzyloxy-5'-bromo)phenyl-1,3-dioxane (10 g, 28.6 mmol) in THF (30 mmol) was added. The mixture was heated and the reaction was initiated with 1,2-dibromoethane (5 drops). The remaining aryl halide solution was added dropwise under reflux. After heating for an additional 30 min, the solution was cooled to r.t. This Grignard solution and a solution of trimethylborate (2.98 g, 28.6 mmol) in THF (30 mL) were added to precooled THF (70 mL, −78 °C) simultaneously over a period of 1 h. The mixture was stirred for another 5 h during which the temperature rose to −40 °C.

The cooling bath was removed and the mixture was stirred for a further 10 min before the reaction was hydrolyzed with 3 M NH_4Cl (10 mL). The mixture was evaporated in vacuo, to the residue was added H_2O (300 mL) and the suspension was acidified (pH 3–4) with 2 M HCl. The mixture was refluxed for 10 min and filtered hot through a filter paper. The filtrate was collected and the residue

including the filter paper was extracted with boiling H_2O (15 × 300 mL containing each 5 drops of 2 M HCl). The combined filtrates were allowed to cool to r. t. to precipitate the product **17**. The solid was filtered by suction and dried in vacuo; yield: 5.13 g (70%); mp 199–200°C.

^{1}H NMR (acetone-d_6/TMS): δ = 5.35 (s, 2 H), 7.20–7.47 (m, 6 H), 7.57 (d, 1 H, J = 8.7 Hz), 7.59 (d, 1 H, J = 1.8 Hz), 8.11 (dd, 1 H, J = 1.8, 8.4 Hz), 8.30 (d, 1 H, J = 1.8 Hz).

4,4′-Dibenzyloxy-3′-[(*S,S*)-*N*-*tert*-butoxycarbonyl)-4-(methoxycarbonyl-2-oxo-1,3-oxazolidin-5-yl]biphenyl-3-carbaldehyde (18):
To a solution of **16** (193 mg, 0.38 mmol) in THF (2 mL) was added **17** (147 mg, 0.57 mmol). After complete dissolution, $(Ph_3P)_4Pd$ (13 mg, 0.12 mmol) was added and the mixture was heated to reflux for 1 h. To the boiling solution, 2 M Na_2CO_3 (250 μL) was added and refluxing was continued for 24 h. The solvent was evaporated, the residue was dissolved in EtOAc (50 mL) and washed with H_2O (10 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Final purification was achieved by MPLC (eluent: hexane/EtOAc, 7:3) yield: 122 mg (50%); $[\alpha]_D^{20}$ + 34.5° (c = 0.29, $CHCl_3$). ^{1}H NMR ($CDCl_3$/TMS): δ = 1.46 (s, 9 H), 3.57 (s, 3 H), 4.66 (d, 1 H, J = 4.4 Hz), 5.15 (s, 2 H), 5.24 (s, 2 H), 5.63 (d, 1 H, J = 4.4 Hz), 7.07 (d, 1 H, J = 8.5 Hz), 7.12 (d, 1 H, J = 8.7 Hz), 7.30–7.54 (m, 11 H), 7.56 (dd, 1 H, J = 2.4, 8.5 Hz), 7.71 (dd, 1 H, J = 2.5, 8.7 Hz), 8.02 (d, 1 H, J = 2.5 Hz), 10.6 (s, 1 H).

4,4′-Dibenzyloxy-3-[(*S*)-2-(*tert*-butoxycarbonylamino)-2-(methoxycarbonyl)-(*R*)-1-hydroxyethyl]biphenyl-3-carbaldehyde (10):
To a stirred solution of **18** (120 mg, 0.19 mmol) in MeOH (50 mL) was added Cs_2CO_3 (10 mg, 0.031 mmol) and stirring was continued for 2 h. The solvent was distilled, the residue was dissolved in Et_2O (50 mL) and washed with 1 M $KHSO_4$ (10 mL). The etheral layer was dried ($MgSO_4$), concentrated and filtered through silica gel (eluent: hexane/EtOAc, 7:3) to give **10**; yield: 93 mg, (80%); $[\alpha]_D^{20}$ + 26.1° (c = 0.80, $CHCl_3$).

The ^{1}H NMR data are identical with the product **10** prepared by BINAP-hydrogenation.

Dipeptide of 3-[(*S*)-2-Amino-2-(methoxycarbonyl)-(*R*)-1-hydroxyethyl]-3′-[(*S*)-2-(benzyloxycarbonylamino)-2-(trimethylsilylethoxycarbonyl)ethyl]-4,4′-dibenzyloxybiphenyl and (*R*)-3-Benzyloxycarbonyl-5-[(*S*)-*N*-*tert*-butoxycarbonylalanin-3-yl]-2,2-dimethyl-1,3-oxazolidine (20):
To a solution of **12** (550 mg, 0.6 mmol) in CH_2Cl_2 (5 mL) was added 6 M HCl in dioxane (5 mL) at 0°C. The mixture was stirred at r. t. for 30 min and concentrated in vacuo. The residue was dissolved in CH_2Cl_2/1 M aq $KHCO_3$ (40 mL, 1:1) and the separated aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. To a solution of the residue were added (*R*)-3-benzyloxycarbonyl-5-[(*S*)-*N*-*tert*-butoxycarbonylalanin-3-yl]-2,2-dimethyl-1,3-oxazoline (**19**; 304 mg, 0.72 mmol), and hydroxybenzotriazole (97 mg, 0.72 mmol) in CH_2Cl_2 (3 mL) and *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) (138 mg, 0.72 mmol) at −10°C. The stirred mixture was warmed to r. t. over 15 h, the solvent evaporated and the residue dissolved in EtOAc (20 mL). The organic phase was washed with 0.5 M H_2SO_4 (3 mL, 0°C) and 1 M aq $KHCO_3$ (10 mL), dried ($MgSO_4$), evaporated and the residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc/CH_2Cl_2, 5:4:1) to afford **20**; yield: 660 mg (91%); $[\alpha]_D^{20}$ + 7.0° (c = 0.7, $CHCl_3$). Compound **20** prepared by the Evans method: $[\alpha]_D^{20}$ + 7.8° (c = 0.9, $CHCl_3$).

^{1}H NMR ($CDCl_3$/TMS): δ = 0.00 (s, 9 H), 0.90 (t, 2 H, J = 8.2 Hz), 1.24–2.08 (m, 17 H), 2.91 (m, 1 H), 3.09 (m, 1 H), 3.28 (m, 1 H), 3.62 (m, 1 H), 3.72 (s, 3 H), 4.00–4.30 (m, 4 H), 4.63 (m, 1 H), 4.95–5.37 (m, 11 H), 5.60–5.80 (m, 2 H), 6.93 (d, 2 H, J = 8.5 Hz), 7.07 (br d, 1 H, J = 9.7 Hz), 7.00–7.65 (m, 24 H).

Dipeptide of 3-[(*S*)-2-Amino-2-(methoxycarbonyl)-(*R*)-1-hydroxyethyl]-3′-[(*S*)-2-benzyloxycarbonylamino)-2-trimethylsilylethoxycarbonyl)ethyl]-4,4′-dibenzyloxybiphenyl and ω-*N*-Benzyloxycarbonyl-(*S*)-2-*N*-*tert*-butoxycarbonyl-(*R*)-4-hydroxyornithine (21a) and Its Diastereoisomer (7*S*,8*R*,11*S*,14*S*,24*R*) (21b):
A solution of **20** (650 mg, 0.54 mmol) in AcOH/H_2O (20 mL, 9:1) was stirred for 4 h at 50°C. The acid was evaporated, the residue was dissolved in EtOAc (30 mL), washed with 1 M aq. $KHCO_3$ (20 mL), dried ($MgSO_4$) and evaporated. Small amounts of the diastereoisomer **21b** (arised by the BINAP hydrogenation) were separated by MPLC (eluent: hexane/EtOAc/CH_2Cl_2, 4:5:1). **21a**, yield: 450 mg (71%); **21b**, yield: 25 mg (4%).

HPLC: $R_{t\,21b}$ = 5.50 min, $R_{t\,21a}$ = 8.35 min (eluent: hexane/EtOAc, 1:1).

21a: $[\alpha]_D^{20}$ + 13.0° (c = 1.9, $CHCl_3$).

^{1}H NMR (DMSO-d_6/TMS): δ = 0.00 (s, 6 H), 0.02 (s, 3 H), 0.83 (t, 2 H, J = 8.4 Hz), 1.31 (s, 9 H), 1.00–1.60 (m, 2 H), 2.78–3.00 (m, 3 H), 3.28 (m,1 H), 3.67 (s, 3 H), 4.01 (m, 1 H), 4.09 (t, 2 H, J = 8.4 Hz), 4.45 (m, 1 H), 4.67 (br, 1 H), 4.89–5.10 (m, 6 H), 5.19 (s, 2 H), 5.22 (s, 2 H), 5.60 (br s, 1 H), 5.94 (br s, 1 H), 6.87 (br d, 1 H, J = 7.9 Hz), 6.95–7.80 (m, 27 H).

The product is identical in every respect with **21a** prepared by the Evans method.

Protected Biphenomycin A (23):
To a stirred solution of **21a** (500 mg, 0.43 mmol in DMF (3 mL) was added $Bu_4NF \cdot 3H_2O$ (272 mg, 0.86 mmol) at r.t. and the mixture was stirred at this temperature for 2 h. After addition of H_2O/EtOAc (30 mL, 1:1), the mixture was acidified with 0.5 M H_2SO_4 (2 mL) at 0°C, the aqueous layer was separated and extracted with EtOAc (2 × 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to give **24**; yield: 440 mg (96%).

To a stirred solution of **24** (440 mg, 0.41 mmol) and pentafluorophenol (83 mg, 0.45 mmol) in CH_2Cl_2 (2 mL) was added EDCI (86 mg, 45 mmol) at −10°C. The solution was warmed to r.t. over 15 h and the solvent was evaporated. The residue was dissolved in EtOAc (20 mL), washed with brine (10 mL), dried ($MgSO_4$) and evaporated. The obtained pentafluorophenyl ester **22** (yield: 505 mg, quant.) was used for the ring closure reaction without further purification. A solution of **22** (505 mg, 0.41 mmol) in CH_2Cl_2 (5 mL) was treated with 6 M HCl in dioxane (5 mL) at 0°C. The mixture was stirred for 30 min at r.t., concentrated in vacuo and the solution of the residue in $CHCl_3$ (40 mL) was added to a well stirred mixture of $CHCl_3$/1 M aq. $KHCO_3$ (200 mL, 1:1) at r.t.. The mixture was stirred at this temperature for 2 h and after further 30 min of stirring at 50°C, the obtained solid was filtered, washed with H_2O (30 mL) and $CHCl_3$ (30 mL) and dried in vacuo to yield **23** (200 mg). The aqueous layer of the filtrate was separated and extracted with hot $CHCl_3$ (3 × 40 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo. The residue was stirred with EtOAc (10 mL) for 10 min and the resulting solid was filtered to give another 150 mg of **23**; total yield: 350 mg (85% from **21a**); mp 282°C (dec); $[\alpha]_D^{20}$ +6.0° (c = 0.58, DMSO), HPLC: R_t = 6.60 min (eluent: EtOAc/hexane, 8:2).

^{1}H NMR (DMSO-d_6/TMS): δ = 1.52 (m, 1 H), 1.89 (m, 1 H), 2.93 (d, 1 H, J = 12.9 Hz), 3.08 (m, 2 H), 3.34 (m,1 H), 3.68 (s, 3 H), 3.72 (m, 1 H), 4.47 (br, 1 H), 4.71 (d, 1 H, J = 9.7 Hz), 4.85 (d, 1 H, J = 12.4 Hz), 4.96 (d, 1 H, J = 12.4 Hz), 4.98 (m, 1 H), 5.03 (s, 2 H), 5.06–5.17 (m, 3 H), 5.22 (s, 2 H), 5.86 (m, 2 H), 6.59 (d, 1 H, J = 7.3 Hz), 7.00–7.12 (m, 3 H), 7.20–7.60 (m, 24 H), 8.63 (d, 1 H, J = 9.6 Hz), 8.72 (d, 1 H, J = 9.1 Hz).

Biphenomycin A (1a):
The protected biphenomycin A **23** (180 mg, 0.19 mmol) was dissolved in hot dioxane (15 mL). After addition of H_2O (2 mL) the mixture was cooled to 10°C and treated with 1 M LiOH (0.2 mL) over a period of 2 h. After stirring for another 30 min, the solvent was evaporated in vacuo. The residue was treated with H_2O (10 mL) and 0.5 M H_2SO_4 (0.5 mL) in an ultrasonic bath at r.t. for 10 min.

The solid was filtered, washed with H_2O (10 mL), Et_2O (10 mL) and dried in vacuo (0.001 mbar) to give the acid **24**; yield: 170 mg (95%). A solution of thioanisole (1.17 mL, 10 mmol) and bromotrimethylsilane (0.13 mL, 1 mmol) in CF_3CO_2H (10 mL) prepared at 0 °C was added to the acid **24** at 0 °C and the mixture was stirred at this temperature for 1 h. The reaction mixture was quenched with Et_2O (60 mL) and stirred for another 10 min at 0 °C. The solid was filtered, washed with Et_2O (3 × 10 mL) and dissolved in water (20 mL). The aqueous solution was washed with EtOAc (5 mL) and concentrated in vacuo. The crude product (120 mg) was purified by preparative HPLC (RP 18, buffered NH_4CO_2H/MeCN, 8:2), buffer: 20 mmol NH_4CO_2H in 1 L H_2O) and the fraction containing product **1a** was freeze dried; yield: 65 mg (70%); mp > 200 °C (dec); $[\alpha]_D^{20}$ − 29° (c = 0.14, 1 M HCl). Natural product: $[\alpha]_D^{20}$ = − 22.5° (c = 0.1, 1 M HCl).

HPLC: R_t = 3.2 min (RP 18; eluent: as previously described for preparative HPLC; natural product: R_t = 3.2 min).

Ion Spray MS: 689 $(M+M)^+$.

^{1}H NMR (D_2O): δ = 1.89–2.14 (m, 2H), 2.97 (dd, 1H, J = 10, 13 Hz), 3.07 (m, 1H), 3.17 (dd, 1H, J = 2.7, 13 Hz); 3.58 (dd, 1H, J = 5.1, 15 Hz), 4.04 (m, 1H), 4.44 (br, 1H), 4.88 (s, 1H), 5.03 (dd, 1H, J = 6.1, 9.8 Hz), 5.84 (s, 1H), 6.95–7.01 (m, 3H), 7.39–8.46 (m, 3H).

The ^{1}H NMR spectrum (D_2O) of the synthetic product **1a** is completely identical with that of a natural sample supplied by Dr. M. Shirahashi.

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